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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/557,586	03/03/2006	Maria Assunta Costa	1136-PCT-US	8745

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/557,586	COSTA ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-10 and 14-28* is/are pending in the application.

4a) Of the above claim(s) *8-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-15 and 17-24* is/are rejected.

7)☒ Claim(s) *16 and 25-28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed on 12/05/2008 is acknowledged.

2. Claims 8-10 and newly added claims 14-28 are pending.

3. Claims 8-10 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 04/17/2008.

4. Claims 14-28 are currently under examination as they read on a multimer protein molecule comprising a plurality of proteins having amino acid sequences selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4 and pharmaceutical compositions comprising said multimer protein.

5. In view of Applicant's amendment filed on 12/05/2008, only the following rejection is maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 14-15 and 17-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (Reference 10; IDS filed on 11/17/2005) in view of Colombo (Reference 7; IDS filed on 11/17/2005).

Vrtala et al. teaches recombinant multimeric protein allergen such as dimer and trimer of major birch pollen allergen Bet vl, (In particular, page 2045 and whole document). The recombinant trimer consisting of three covalently linked copies of the allergens is useful for inducing IgG antibodies in vivo (pharmaceutical composition, for medical use as a hypoallergenic agent, comprising diluents) and blocking IgE binding to Bet vl and related allergens, (In particular, abstract and page 2047).

The claimed invention differs from the prior art in the recitation of "a multimer protein molecule comprising a plurality of proteins having amino acid sequences selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4" of claim 14; "wherein a first amino acid sequence consists of SEQ ID NO:1 of a *Parietaria judaica* major allergen Par j 1 and a second amino acid sequence consists of SEQ ID NO: 3 of a Parietaria judaica major allergen Par j 2" of claim 15; "the multimer protein molecule according to claims 14 or 15 for medical use" of claims 17and 21; "the multimer protein molecule according to claims 14 or 15 for medical use as a hypoallergenic agent" of claim 18 and 22; a "pharmaceutical composition comprising an effective and acceptable amount of the multimer protein molecule according to claims 14 or 15 and suitable adjuvants or diluents of claims 19 and 23; and "a

composition comprising the multimer protein molecule" according to claim 14 or 15 of claims 20 and 24.

Colombo et al teaches Par j 1 and Par j2 allergens consisting of SEQ ID NOs 1 and 3 and loop 1 allergen mutant of Par j 1 consisting of SEQ ID NO:2 in a pharmaceutical composition for medical use comprising 1X PBS (diluent) for diagnosis and therapy of pollen allergy (In particular, pages 199-200 'Materials and Methods', sequences in Table 2, whole document). The reference also teaches that the loop 1 allergen mutant of Par j 1 consisting of SEQ ID NO:2 was generated as a hypoallergenic derivative of an allergen for specific immunotherapy (In particular, last sentences of first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Par j 1, Par j2 and mutant Par j1 allergens taught by Colombo in the major birch pollen allergen Bet vl hypoallergenic dimers and trimers of Vrtala et al because Vrtala et al. teaches that the dimers and trimers are useful for diagnosis and/or treating allergy, particularly because they induce IgG and block IgE. Colombo et al. teaches that Par j 1, Par j2 and mutant Par j1 allergens can themselves be useful for diagnosis and therapy of Parietaria pollen allergy, so it would be obvious to generate hypoallergenic multimers of the Parietaria allergens for diagnosis and therapy as well. In addition, one of ordinary skill in the art would have had a high expectation of success in practicing the method Vrtala et al. with the allergens of Colombo et al. because both references teach using hypoallergenic allergens for pharamceutical use. In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is

prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Applicant's argument filed on 12/05/2008 has been fully considered, but is not found persuasive.

Applicant argues:

> Vrtala et al. teaches the formation, by genetic engineering, of a homo-dimer or trimer of the major birch pollen allergen (Bet Vl), a tree pollen allergen unrelated to the Par j allergen of the present invention. The multimers consist of covalently linked copies of the allergen Bet v I. The multimers were obtained by expressing 2 or 3 copies of Bet v 1 cDNA linked by short oligonucleotide spacers with an open reading frame, in E. coli (p. 2045, left column, second paragraph, first sentence). Vrtala et al. neither teaches that different allergens may be combined to generate an hetero-dimer or trimer, nor does Vrtala teach what properties a multimer of different allergens would have.
>
> In addition, there does not exist sufficient motivation for persons of ordinary skill in the art to combine the teaching of Vrtala et al. to that of Columbo, because the documents relate to different technical fields. Nevertheless, if the teachings of Vrtala et al. and Columbo were combined, there would not be a reasonable chance of success with respect to a person of ordinary skill in the art deriving the present invention, which relates i) to different allergens than Bet v 1 and ii) to heterodimers, the molecules displaying hypoallergenicity. Therefore, such a combination would not have been ~obvious to try."
>
> Moreover, in the field of allergens, it is notoriously difficult to predict whether an engineered allergen may have hypoallergenic properties and the engineering of an allergen is not an obvious task. The skilled person in this field is well aware that even a small structural change in the product (a vector, a

protein, a DNA sequence) or in the procedure (purification process) can produce dramatic functional changes.

For instance, the publication Bonura et al., herein enclosed as Exhibit 1 (IAAI 2001, 9 pages), teaches that site specific mutagenesis on cysteine residues of the Parj 1 allergens is a powerful strategy to modify the stucture of an allergen, leading to reduced IgE binding activity. However, not all the introduced mutations displayed an immunological effect. In particular, when cysteines 4, 29 and 30 were disrupted, a highly reduced IgE binding activity in vitro and in vivo was observed; on the contrary, when cysteines 50 and 52 were disrupted no biological effect was obtained. Thus, disruption of disulphide bonds cannot be used as a general strategy to reduce the allergenicity of a molecule. This is in no way obvious and predictable.

In the present invention, two independent allergens with independent IgE epitopes Duro et al. FEBS Letters 199 (4 pages), herein enclosed as Exhibit 2 were combined rendering their engineering even more complex and unpredictable. Thus, the multimers of the present invention are not obvious in view of cited documents. "

It is the Examiner's position that Vrtala and et al. and Columbo et al. do not relate to different technical fields. Both references are directed to allergens, allergen immunotherapies and the generation of hypoallergenic compositions for specific immunotherapy. While it is true, as evidenced by the Bonura reference, that it is difficult to predict what allergen mutants will have hypoallergenic properties, the Vrtala reference teaches that the generation of a multimer makes Bet v 1 exhibit reduced IgE binding for reasons other than changes to secondary structure. In addition, the reference specifically teaches that the method may be used as a model to generate other hypoallergenic multimers to be used in allergy vaccination (In particular, right column on page 2047). Therefore, it is obvious to use the technique with other pollen allergens, such as Par j 1 and Par j 2. The Duro et al. reference teachings are not relevant or persuasive to support the contention of non-obviousness.

8. Claims 16 and 25-28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 26, 2009
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